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ORIGINAL RESEARCH

Anticoagulant Therapy in Initially Low-Risk Patients With Nonvalvular Atrial Fibrillation Who Develop Risk Factors

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BACKGROUND: The CHA_2DS_2-VASc score has been validated for stroke risk prediction in patients with atrial fibrillation (AF). Antithrombotic therapy is not recommended for low-risk patients with AF (CHA_2DS_2-VASc 0 [male] or 1 [female]). We studied a cohort of initially low-risk patients with AF in relation to their development of incident comorbidities and their treatment on oral anticoagulation therapy.

METHODS AND RESULTS: We assessed data from 14 441 low-risk patients with AF (CHA_2DS_2-VASc score of 0 [male] or 1 [female]) using the Korean National Health Insurance Service database, in relation to their development of incident stroke risk factors and adverse outcomes. The clinical end point was the occurrence of ischemic stroke, major bleeding, all-cause death, or the composite outcome (ischemic stroke + major bleeding + all-cause death). In our cohort, 2615 (29.1%) male and 1650 (30.3%) female patients acquired at least 1 new stroke risk factor during a mean follow-up of 2.0 years. Among the patients with an increasing CHA_2DS_2-VASc score ≥1, male and female patients treated with oral anticoagulants had a significantly lower risk of ischemic stroke (male: hazard ratio [HR], 0.62 [95% CI, 0.44–0.82; *P*=0.003]; female: HR, 0.65 [95% CI, 0.47–0.84; *P*=0.007]), all-cause death (male: HR, 0.67 [95% CI, 0.49–0.88; *P*=0.009]; female: HR, 0.82 [95% CI, 0.63–1.02; *P*=0.185]), and composite outcomes (male: HR, 0.78 [95% CI, 0.61–0.95; *P*=0.042]; female: HR, 0.79 [95% CI, 0.62–0.96; *P*=0.045]) than patients not treated with oral anticoagulants.

CONCLUSIONS: Approximately 30% of patients acquired ≥1 stroke risk factor over a 2-year follow-up period. Low-risk patients with AF should be regularly reassessed to adequately identify those with incident stroke risk factors that would merit thromboprophylaxis for the prevention of stroke and the composite outcome.

Key Words: anticoagulant ■ atrial fibrillation ■ death ■ intracranial hemorrhage ■ stroke

Atrial fibrillation (AF) is a major cause of ischemic stroke, and AF-related stroke has a worse prognosis and a higher recurrence rate than non–AF-related stroke.[1] Most international guidelines recommend the use of the CHA_2DS_2-VASc (congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, stroke/transient ischemic attack, vascular disease, age 65–74 years, sex category) score for stroke risk stratification, including those from the Asia Pacific Heart Rhythm Society and other Asian countries.[2–6]

Although there are many similarities in the recommendations for antithrombotic therapy in these guidelines, the consensus is that antithrombotic therapy is not recommended for low-risk patients with AF (ie, CHA_2DS_2-VASc score of 0 [male] or 1 [female]) without nonsex stroke risk factors. In many published studies, the CHA_2DS_2-VASc score is conventionally calculated for baseline risk factors, but the risk score would be increased during the follow-up period, between 1 and 10 years (or

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CLINICAL PERSPECTIVE

What Is New?

- We studied a cohort of initially low-risk patients with AF (CHA_2DS_2-VASc score of 0 [male], 1 [female]) in relation to their development of incident comorbidities and their treatment on oral anticoagulation therapy.
- We show that approximately 30% of low-risk AF patients acquire new risk factors over 2 years.
- Patients should be reassessed regularly to adequately identify those with incident stroke risk factors that would merit thromboprophylaxis for the prevention of stroke and the composite outcome (ischemic stroke, major bleeding, all-cause death).

What Are the Clinical Implications?

- In this analysis of a large cohort of low-risk patients with AF who were not on oral anticoagulant therapy at baseline, patients with ≥1 new-onset risk factor who were subsequently treated with an oral anticoagulant at follow-up had significantly lower event rates of ischemic stroke and the composite clinical outcome compared with those not treated with oral anticoagulants.

Nonstandard Abbreviations and Acronyms

AF	atrial fibrillation
HR	hazard ratio
ICD-10-CM	*International Classification of Diseases, Tenth Revision, Clinical Modification*
IQR	interquartile range
NHIS	National Health Insurance Service
NOAC	non–vitamin K antagonist oral anticoagulant
OAC	oral anticoagulant

more). Because AF patients get older and acquire more new comorbidities over time, they would no longer be low risk. In addition, age is probably the most important risk factor for ischemic stroke in AF among individual risk factors, particularly for "low-risk" patients,[7] and about 90% develop ≥1 new stroke risk factor before presentation with ischemic stroke.[8]

The objective of this study was to investigate a cohort of low-risk patients with AF in relation to their development of incident comorbidities and their use of oral anticoagulation therapy.

METHODS

The data that support the findings of this study are available from the corresponding author on reasonable request.

Overall, 14 441 nonvalvular patients with AF aged ≥20 years out of a total of 363 188 patients from January 2013 to December 2017 were selected from the National Health Insurance Service (NHIS) database as the study population. Prevalent nonvalvular AF was identified using the *International Classification of Diseases, Tenth Revision, Clinical Modification* (*ICD-10-CM*) code (I48) and baseline absence of mitral stenosis or mechanical heart valves (*ICD-10-CM* codes I05 or Z952–Z954). We excluded patients who had a history of thromboembolic events or intracranial hemorrhage and included only patients with newly diagnosed AF. Patients receiving oral anticoagulants (OAC; warfarin or non–vitamin K antagonist OAC), aspirin, or other antiplatelet agents at baseline were also excluded. To establish a low-risk patient population, male patients with a CHA_2DS_2-VASc score of ≥1 and female patients with a CHA_2DS_2-VASc score of ≥2 were excluded. A flowchart of study enrollment is shown in Figure 1.

In this study, patients were censored at discontinuation of the initial OAC or on switching to a different OAC. We defined discontinuation as having no additional refill for at least 60 days since the end of supply for a prescription. Approval for this study was obtained from the ethics review board of Dong-A University Hospital (number 15–130), and informed consent was waived.

Clinical End Points

The clinical end point was the occurrence of ischemic stroke (*ICD-10-CM* codes I63 or I64), intracranial hemorrhage (*ICD-10-CM* codes I60–62) or hospitalization for gastrointestinal bleeding (*ICD-10* codes K22.6, K25.0, K25.2, K25.4, K25.6, K26.0, K26.2, K26.4, K26.6, K27.0, K27.2, K27.4, K27.6, K28.0, K28.2, K28.4, K28.6, K29.0, K62.5, K92.0, K92.1, K92.2) for major bleeding, and all-cause death during the follow-up period. A composite clinical outcome (ischemic stroke, major bleeding, all-cause death) was also assessed. Clinical outcomes were determined according to OAC use or non-OAC use during follow-up. Non-OAC use could include no antithrombotic therapy or aspirin; the latter drug is not recommended for stroke prevention because it is ineffective and unsafe in patients with AF.[2–6]

Statistical Analysis

Continuous variables are expressed as mean values with standard deviations, and categorical variables

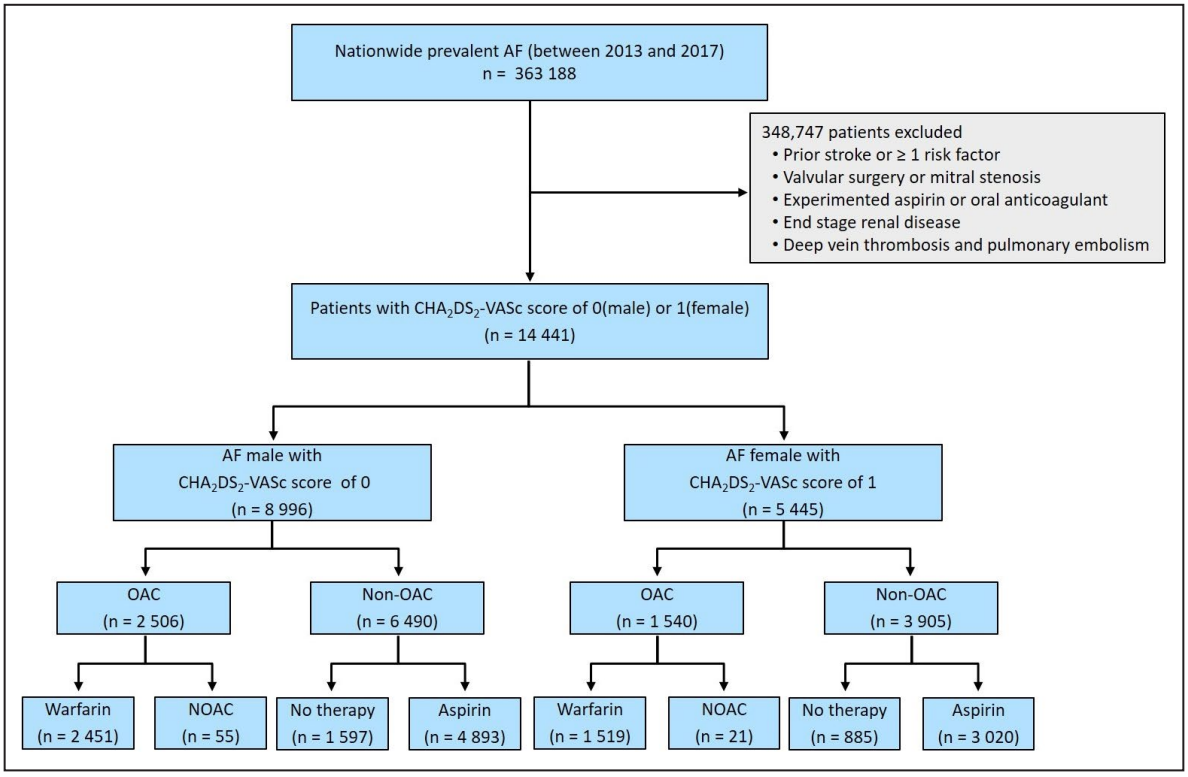

Figure 1. Flowchart of study enrollment.
AF indicates atrial fibrillation; NOAC, non-vitamin K antagonist oral anticoagulant; non-OAC, no antithrombotic therapy or aspirin (vitamin K antagonist oral anticoagulant); and OAC, oral anticoagulant.

are presented as frequencies (percentages). For the clinical end points, we calculated incidence rates per 100 person-years, and estimated CIs for the incidence rates assuming that the number of cases followed a Poisson distribution. The risk of events was assessed using the Cox proportional hazards analysis.

Table 1. Characteristics of AF Patients With Baseline CHA_2DS_2-VASc Scores of 0 (Male) or 1 (Female)

	Total	CHA_2DS_2-VASc score 0 (male)		CHA_2DS_2-VASc score 1 (female)	
		OAC	Non-OAC	OAC	Non-OAC
	N=14 441	n=2506	n=6490	n=1540	n=3905
Age, y	54.3±9.7	54.1±10.1	53.9±10.2	54.3±9.6	54.6±9.9
<55	6806 (47.1)	1052 (42.0)	3123 (48.1)	686 (44.6)	1945 (49.8)
55–64	7635 (52.9)	1454 (58.0)	3367 (51.9)	854 (55.4)	1960 (50.2)
Clinical history					
Dyslipidemia	3103 (21.5)	461 (18.4)	1428 (22.0)	306 (19.8)	908 (23.3)
Chronic lung disease	1241 (8.6)	203 (8.1)	556 (8.6)	140 (9.1)	342 (8.7)
Medication					
Aspirin			4893 (66.1)		3020 (66.2)
Warfarin		2451 (33.1)		1519 (33.3)	
NOAC		55 (0.7)		21 (0.5)	
Rivaroxaban		29 (0.4)		11 (0.2)	
Dabigatran		13 (0.2)		5 (0.1)	
Apixaban		8 (0.1)		3 (0.1)	
Edoxaban		5 (0.1)		2 (0.04)	
Follow-up, y, median (IQR)	2.1 (1.4–2.4)	2.0 (1.5–2.6)	2.2 (1.5–2.5)	2.0 (1.4–2.5)	2.1 (1.5–2.6)

Values are n (%) or mean±SD, except as noted. Non-OAC indicates no antithrombotic therapy or aspirin. AF indicates atrial fibrillation; IQR, interquartile range; NOAC, non–vitamin K antagonist oral anticoagulant; and OAC, oral anticoagulant (warfarin or non–vitamin K antagonist oral anticoagulant).

Table 2. Characteristics of AF Patients With and Without ≥1 New-Onset Stroke Risk Factor

	Total	With ≥1 new-onset risk factor (male)		With ≥1 new-onset risk factor (female)		Total	Without new-onset risk factor (male)		Without new-onset risk factor (female)	
		OACs	Non-OACs	OACs	Non-OACs		OACs	Non-OACs	OACs	Non-OACs
	n=4265	n=793	n=1822	n=494	n=1156	n=10 176	n=1713	n=4668	n=1046	n=2749
Age, y	55.2±9.7	54.9±9.4	54.7±9.5	55.1±9.4	54.6±9.4	55.3±9.4	55.2±9.4	54.9±10.1	55.2±9.1	55.5±9.4
<55	1873 (43.9)	324 (40.9)	818 (44.9)	209 (42.3)	522 (45.1)	4933 (48.5)	699 (40.8)	2332 (50.0)	472 (45.1)	1430 (52.0)
55–64	2392 (56.1)	469 (59.1)	1004 (55.1)	285 (57.7)	634 (54.9)	5243 (51.5)	1014 (59.2)	2336 (50.0)	574 (54.9)	1319 (48.0)
Clinical history										
Dyslipidemia	966 (22.6)	155 (19.5)	427 (23.4)	103 (20.8)	281 (24.3)	2137 (21.0)	314 (18.3)	1014 (21.7)	197 (18.8)	612 (22.3)
Chronic lung disease	394 (9.2)	65 (8.2)	175 (9.6)	47 (9.5)	107 (9.3)	847 (8.32)	129 (7.5)	379 (8.1)	93 (8.9)	246 (8.9)
New-onset comorbidities										
Age ≥65 y	1498 (35.1)	266 (33.5)	655 (35.9)	170 (34.4)	407 (35.2)					
Hypertension	1666 (39.1)	301 (37.9)	714 (39.2)	190 (38.4)	461 (39.9)					
CHF	832 (19.5)	152 (19.2)	354 (19.5)	94 (19.1)	230 (19.9)					
Diabetes mellitus	542 (12.7)	96 (12.2)	235 (12.9)	60 (12.2)	149 (12.9)					
Vascular disease	486 (11.4)	88 (11.1)	208 (11.4)	56 (11.3)	134 (11.6)					
Medication										
Aspirin			1424 (64.2)		913 (64.9)			3469 (66.9)		2118 (67.2)
Warfarin		752 (33.9)		480 (34.1)			1699 (32.8)		1039 (33.0)	
NOAC		41 (1.9)		14 (1.0)			14 (0.3)		7 (0.2)	
Rivaroxaban		21 (1.0)		7 (0.5)			8 (0.2)		4 (0.1)	
Dabigatran		10 (0.4)		3 (0.2)			3 (0.1)		2 (0.1)	
Apixaban		6 (0.3)		2 (0.1)			2 (0.04)		1 (0.03)	
Edoxaban		4 (0.2)		1 (0.1)			1 (0.02)		1 (0.03)	
Follow-up, y, median (IQR)	2.0 (1.4–2.4)	2.0 (1.4–2.5)	2.1 (1.5–2.5)	1.9 (1.4–2.4)	2.0 (1.4–2.5)	2.0 (1.4–2.4)	2.0 (1.4–2.5)	2.0 (1.5–2.5)	1.9 (1.4–2.4)	2.0 (1.4–2.5)

Values are n (%) or mean±SD, except as noted. Non-OAC indicates no antithrombotic therapy or aspirin. AF indicates atrial fibrillation; CHF, congestive heart failure; IQR, interquartile range; NOAC, non–vitamin K antagonist oral anticoagulant; and OAC, oral anticoagulant (warfarin or non–vitamin K antagonist oral anticoagulant).

Cumulative incidences of clinical end points were constructed as Kaplan–Meier estimates according to the therapy used and were compared using the log-rank test. All reported *P* values are 2-sided, and $P<0.05$ was considered statistically significant. Data manipulation and statistical analyses were conducted using SAS v9.3 (SAS Institute).

Results

Table 1 summarizes the characteristics of the 14 441 patients with AF (CHA_2DS_2-VASc score of 0 [male] or 1 [female]) who were included in the analysis: 8996 (62.2%) were male. Among 14 441 patients with AF, 4046 (28.0%; ie, 2506 male [27.9%] and 1540 female [28.3%]) received OACs during follow-up. The median follow-up duration was 2.1 years (interquartile range, 1.4–2.4) in total patients.

Changes in CHA_2DS_2-VASc Score

Among a total of 14 441 initially low-risk patients with AF, increasing CHA_2DS_2-VASc scores ≥1 were found in 2615 (29.1%) male and 1650 (30.3%) female patients with AF during a median follow-up of 2.2 years (Table 2). Of the study cohort, 4265 patients with AF acquired ≥1 new comorbidity with an annual risk of 13.9% per year for increasing CHA_2DS_2-VASc score (risk/year: 6.72% for hypertension, 5.64% for age ≥65 years, 2.53% for congestive heart failure, 1.97% for diabetes mellitus, 1.17% for vascular diseases) (Table 3). The cumulative incidence rate for increasing CHA_2DS_2-VASc scores ≥1 are shown in Figure 2.

OAC Use Compared With Non-OAC Use

Rates of ischemic stroke, major bleeding, all-cause death, and composite outcomes (ischemic stroke, major bleeding, all-cause death) in relation to OAC and non-OAC use among patients with AF and baseline low risk (CHA_2DS_2-VASc score of 0 [male] or 1 [female]) are shown in Figure 3. During median follow-up of 2.1 years, the annual ischemic stroke rates for non-OAC and OAC use by male groups with baseline CHA_2DS_2-VASc score of 0 were 0.72% and 0.49%, respectively. During follow-up, the annual incidence of ischemic stroke was 0.85% and 0.72% for non-OAC and OAC use by female groups with a baseline CHA_2DS_2-VASc score of 1, respectively.

In patients with ≥1 new-onset risk factor, the incidence rates of ischemic stroke in men were 1.43% and 0.92% per year for the non-OAC and OAC groups, respectively. In female patients, the incidence rates of ischemic stroke were 1.51% and 1.11% per year for non-OAC and OAC users, respectively. Male and female patients using OACs (hazard ratio, 0.62 [95% CI, 0.44–0.82; *P*=0.003] and 0.65 [95% CI, 0.47–0.84; *P*=0.007], respectively) had significantly lower risk of ischemic stroke than non-OAC users. However, rates of major bleeding (intracranial hemorrhage or hospitalization for gastrointestinal bleeding) increased in OAC users compared with non-OAC users (per year, male: 2.03% versus 1.57%; female: 1.96% versus 1.52%). Consequently, OAC use was associated with higher risk of major bleeding than non-OAC use (male: HR, 1.48 [95% CI, 1.29–1.67; *P*=0.008]; female: HR, 1.47 [95% CI, 1.28–1.66; *P*=0.009]). The incidence rates of all-cause death in male patients were 1.71% and 1.29% per year for non-OAC and OAC users, respectively. The rates of all-cause death in non-OAC- and OAC-treated female patients were 1.54% and 1.30% per year, respectively. OAC use was associated with lower risk of all-cause death compared with non-OAC use in male patients (HR, 0.67; 95% CI, 0.49–0.88; *P*=0.009) but not female patients (HR, 0.82; 95% CI, 0.63–1.02; *P*=0.185).

In both male and female patients with ≥1 new-onset risk factor, there was a reduction in the annual risk of the composite outcome (ischemic stroke, major bleeding, and all-cause death) with OAC use (4.18% and 4.21% per year, respectively) compared with non-OAC use (4.55% and 4.49% per year, respectively). OAC use was associated with better composite outcome in both male patients (HR, 0.78; 95% CI, 0.61–0.95; *P*=0.042) and female patients (HR, 0.79;

Table 3. Annual risks of ≥1 new-onset comorbidity

New-onset comorbidity	Annual IR (95% CI)		
	Total (n=4265)	Male (n=2615)	Female (n=1650)
Age ≥65 y	5.64 (5.07–6.21)	5.51 (4.94–6.08)	5.71 (5.15–6.27)
Hypertension	6.72 (6.11–7.33)	6.63 (6.02–7.24)	6.81 (6.19–7.43)
Diabetes mellitus	1.97 (1.51–2.43)	1.89 (1.43–2.35)	2.01 (1.57–2.46)
CHF	2.53 (1.84–3.22)	2.49 (1.80–3.18)	2.71 (2.02–3.40)
Vascular disease	1.17 (0.71–1.63)	1.27 (0.81–1.73)	1.42 (0.96–1.89)
Any	13.89 (13.36–14.42)	12.93 (12.40–13.46)	14.52 (13.98–15.06)
Follow-up, y, median (IQR)	2.16 (1.47–2.89)	2.13 (1.44–2.85)	2.21 (1.50–2.93)

CHF indicates congestive heart failure; IR, incidence rate (events divided by 100 person-years, percentage per year); and IQR, interquartile range.

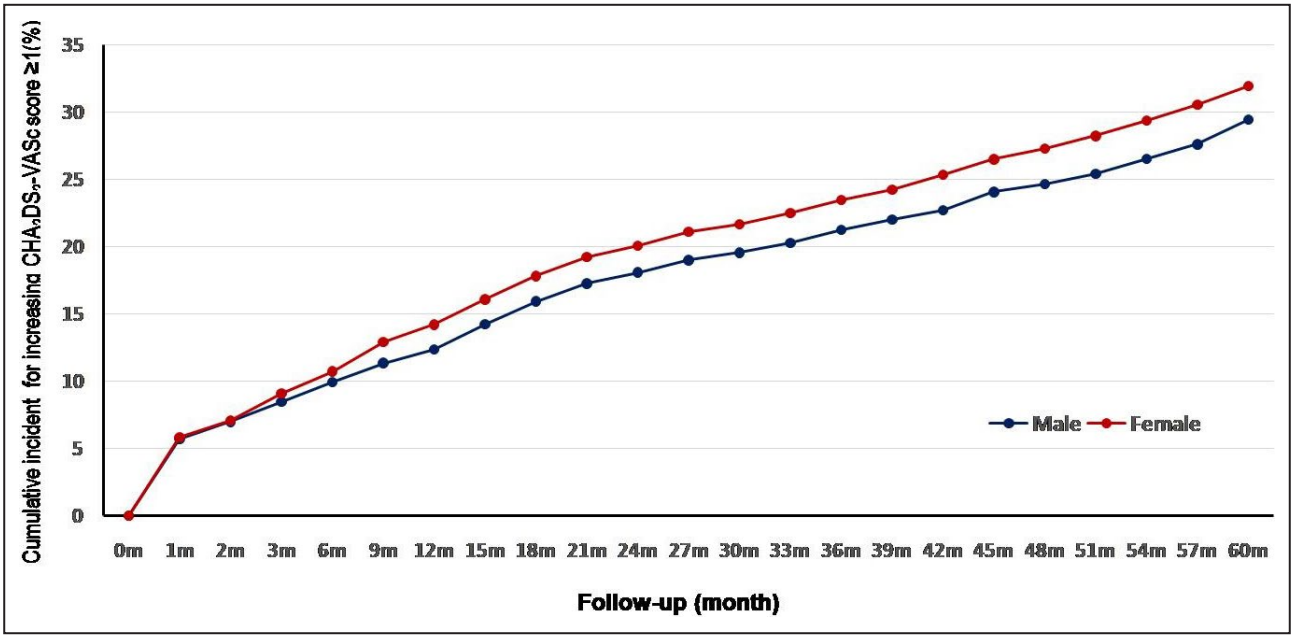

Figure 2. Cumulative incidence rate for increasing CHA_2DS_2-VASc score ≥1.

95% CI, 0.62–0.96; *P*=0.045) with ≥1 new-onset risk factor compared with non-OAC users (Figure 4). The cumulative incidence of the clinical outcomes is shown in Figures 5 and 6.

DISCUSSION

In this analysis of a large cohort of low-risk patients with AF(CHA_2DS_2-VASc score of 0 [male] or 1 [female])

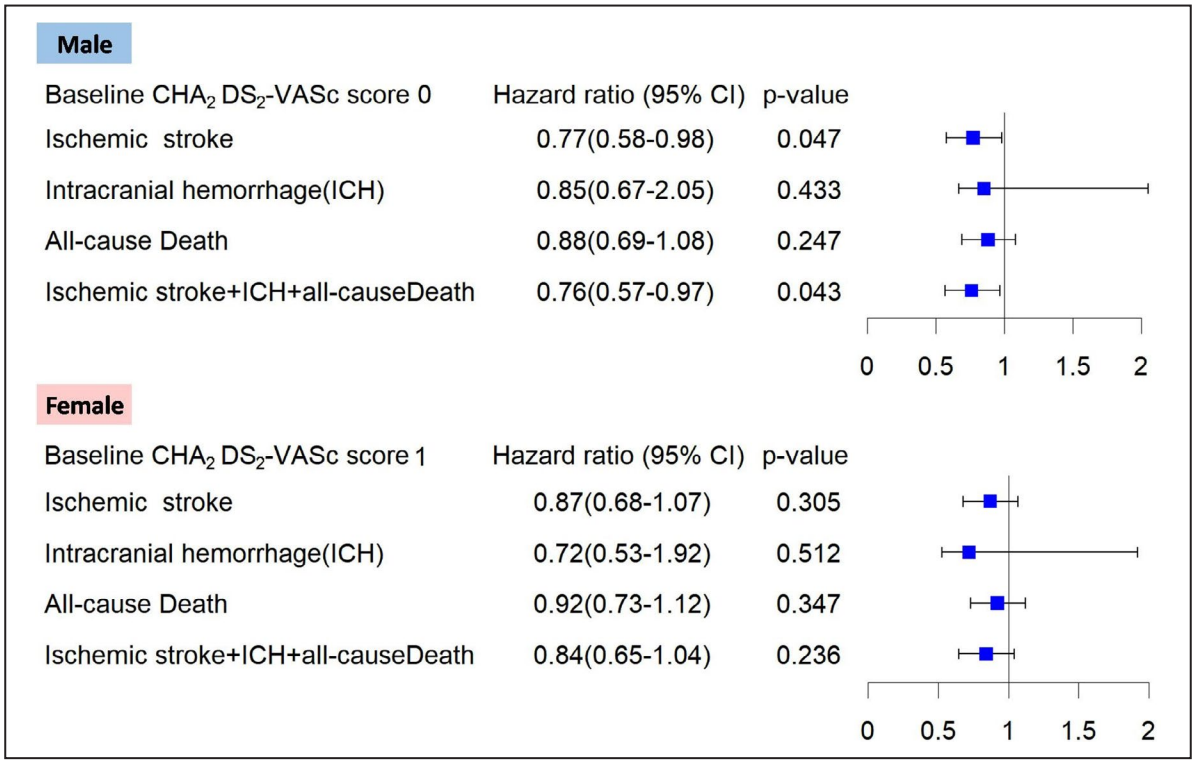

Figure 3. Event rates for OAC use compared with non-OAC use in patients with atrial fibrillation with a baseline CHA_2DS_2-VASc score of 0 (male) or 1 (female).
IR, incidence rate (events divided by 100 person-years, percentage per year); and OAC, oral anticoagulant.

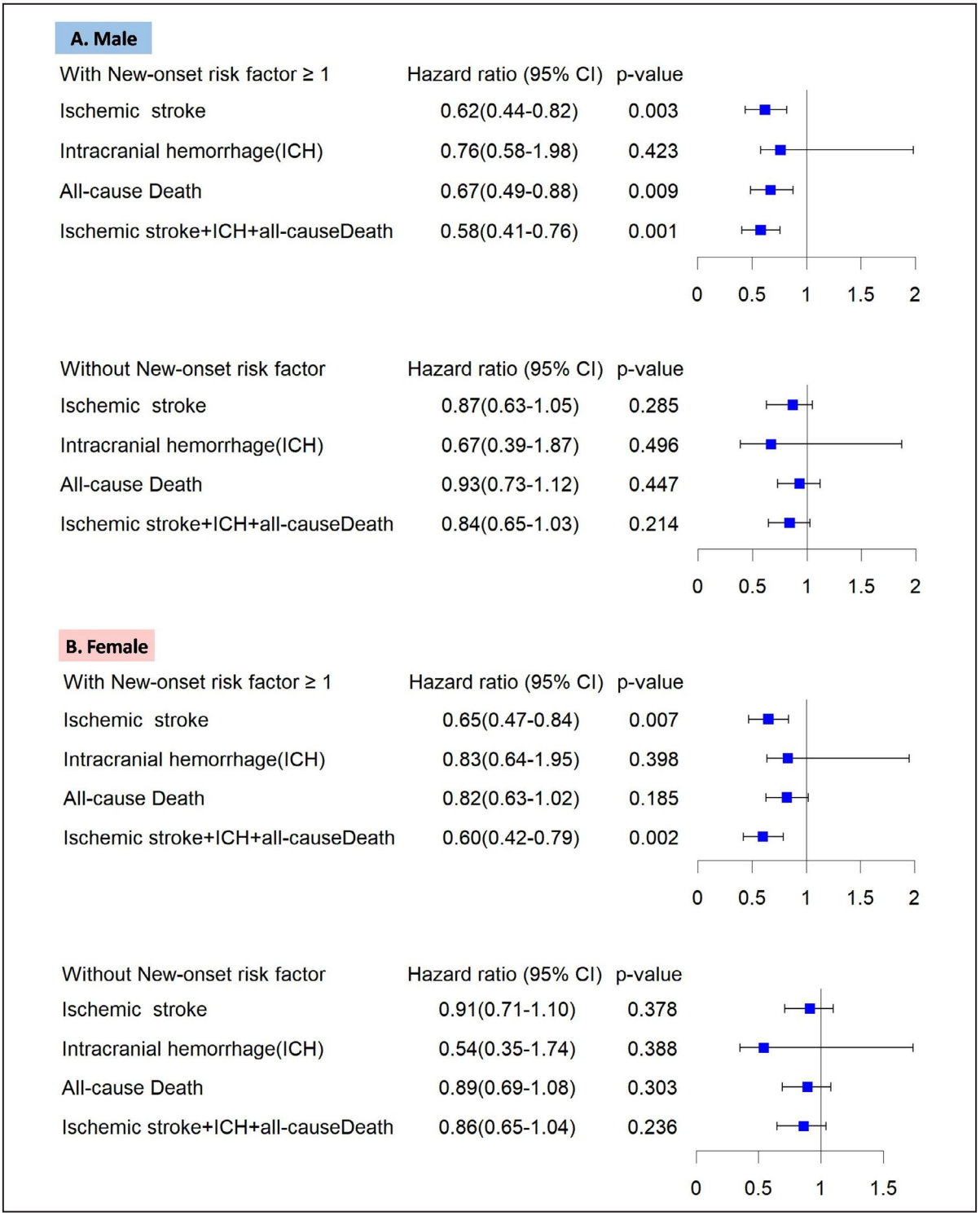

Figure 4. Event rates for OAC use compared with non-OAC use in patients with atrial fibrillation and ≥1 new-onset risk factor. Male (A) or female (B).
IR, incidence rate (events divided by 100 person-years, percentage per year); and OAC, oral anticoagulant.

who were not on OAC therapy at baseline, patients with ≥1 new-onset risk factor subsequently treated with OACs at follow-up had significantly lower event rates of ischemic stroke and composite clinical outcomes (ischemic stroke, major bleeding, all-cause death) compared with non-OAC users. This study provides the first report of a significant benefit with antithrombotic therapy in patients with AF who have ≥1 incident

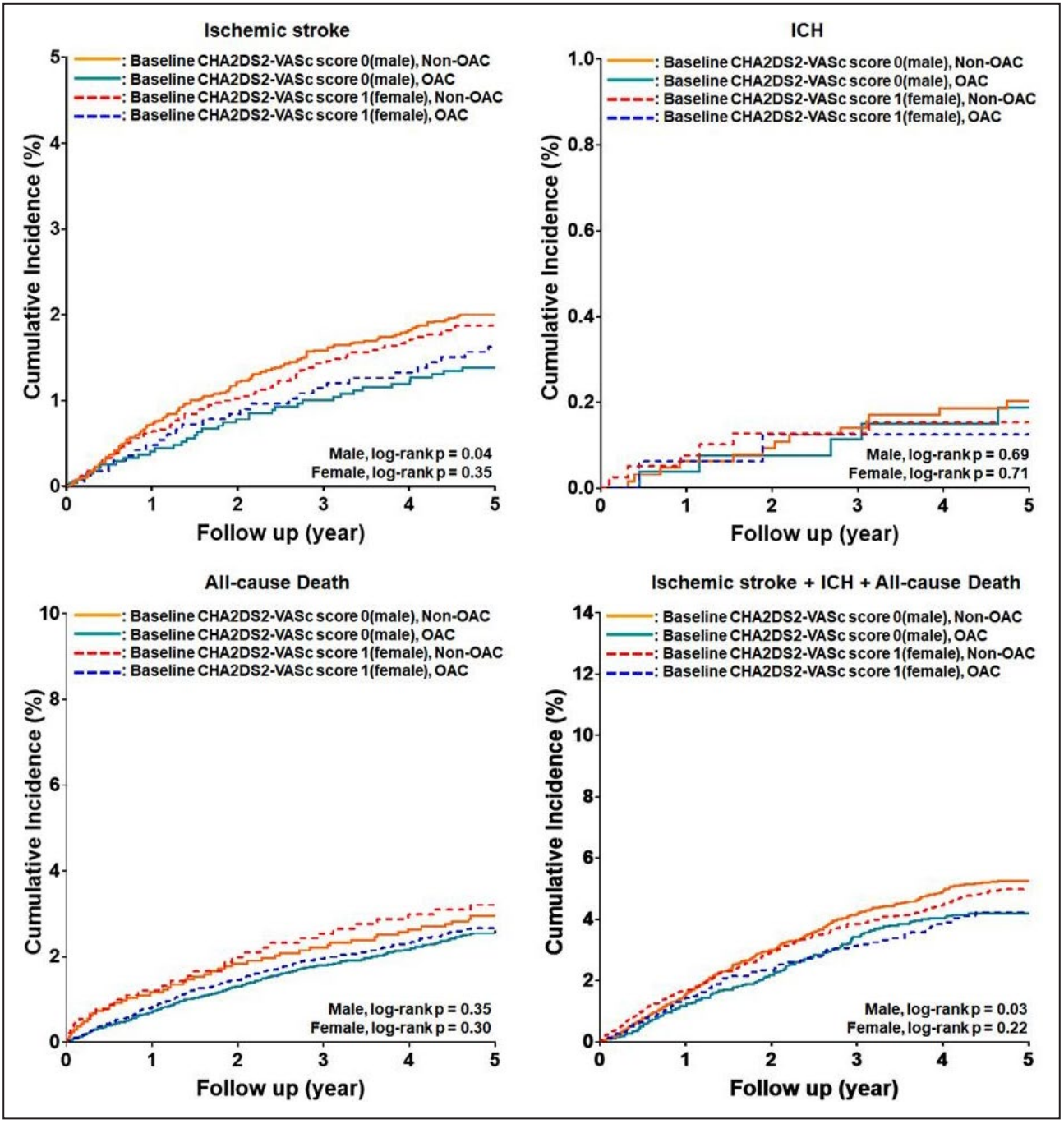

Figure 5. Cumulative incidence of clinical outcomes according to OAC therapy in patients with atrial fibrillation and a baseline CHA_2DS_2-VASc score of 0 (male) or 1 (female).
OAC indicates oral anticoagulant.

nonsex CHA_2DS_2-VASc risk factor. Of note, approximately 13.9% of patients with AF per year would have an increasing CHA_2DS_2-VASc score ≥1 with new comorbidities acquired during follow-up, the most common being hypertension.

International guidelines suggest that antithrombotic therapy is not recommended for low-risk patients with AF (ie. CHA_2DS_2-VASc score of 0 [male] or 1 [female]) without nonsex stroke risk factors.[2–6] The 2006 American College of Cardiology and American Heart Association AF guidelines and the 2018 CHEST (American College of Chest Physicians) guidelines state that individual risk varies over time, so the need for anticoagulation must be reevaluated periodically in all patients with AF.[9] This step is particularly important for low-risk patients with AF at baseline because these patients usually do not receive OAC therapy when AF is diagnosed. However, new

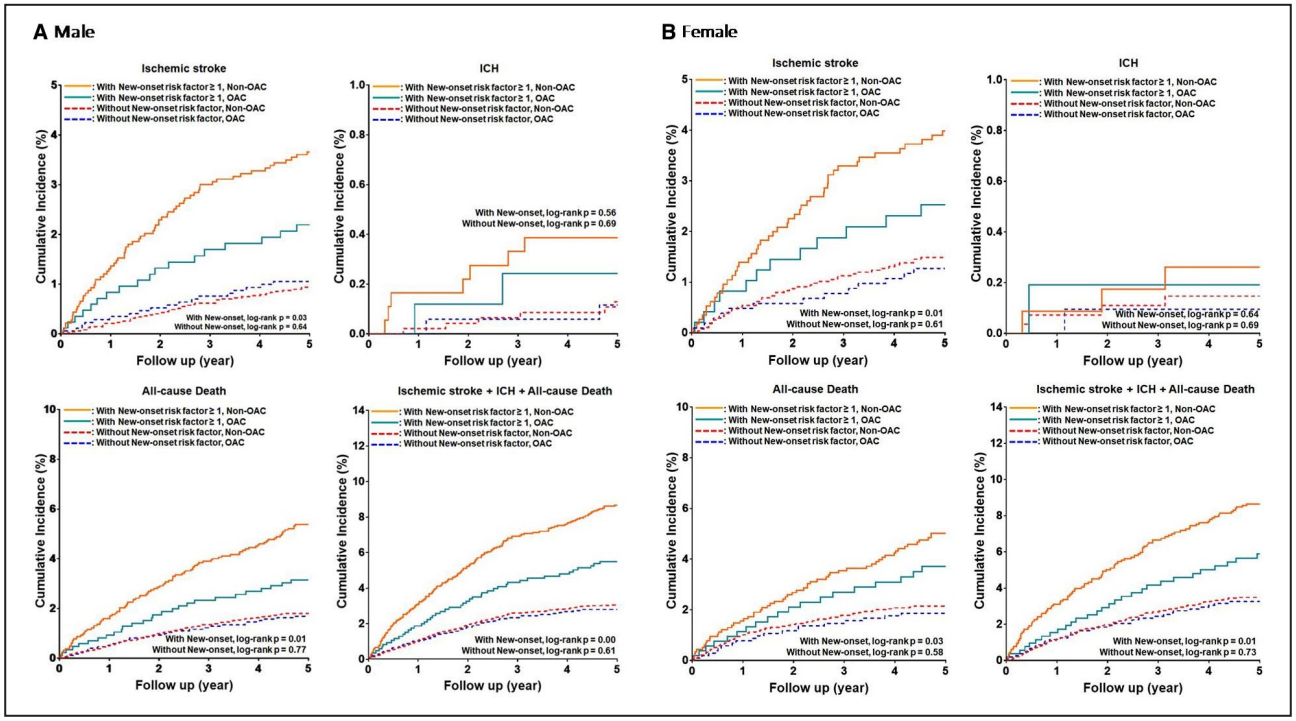

Figure 6. Cumulative incidence of clinical outcomes according to OAC therapy in patients with atrial fibrillation and ≥1 or 0 new-onset risk factor: male (A) or female (B).
OAC indicates oral anticoagulant.

comorbidities could develop thereafter that could substantially increase the risk of ischemic stroke.

Indeed, stroke risk of patients with AF is not static. The CHA_2DS_2-VASc score could increase as patients get older and accumulate more comorbidities.[8] In addition, the 2018 CHEST guidelines and the 2019 focused update of the American College of Cardiology, the American Heart Association, and the Heart Rhythm Society AF guidelines both recommend the reassessment of stroke risk and the need for anticoagulant therapy at periodic intervals.[5,10] Data from the current study show that CHA_2DS_2-VASc score should be regularly reassessed for optimizing stroke prevention with antithrombotic therapy.[11,12] The current age threshold for OAC treatment (age <65 years) that defines "low risk" has even been proposed to be lowered to age <50 or <55 years among Asian patients.[13,14]

In this study, the annual ischemic stroke rates for non-OAC-treated male patients (CHA_2DS_2-VASc score of 0) and female patients (CHA_2DS_2-VASc score of 1) were 0.72% and 0.85% per year, respectively; these rates are well below the treatment threshold for OAC.[1] However, among non-OAC users with increasing CHA_2DS_2-VASc scores ≥1, the annual risk of ischemic stroke was increased to 1.43% per year for men and 1.51% per year for women, which is above the stroke rate threshold where OAC use is beneficial.[1] In addition, OAC use significantly decreased the risk of ischemic stroke and composite clinical outcome compared with non-OAC use.

Study Limitations

First, this study is based on a nationwide cohort study using Korean NHIS data and may be limited by errors of coding, missing data, and laboratory measurements. Furthermore, because AF diagnoses and the estimation of clinical outcomes were based on diagnostic codes registered by the physicians, the diagnosis of AF and events could be inaccurate. Second, the registry data also fail to provide any details regarding drug changes over time and some unmeasurable confounding factors such as physician decision. For this reason, in the main analysis, we sought to adjust for several lists of potential confounders by including the confounders in the Cox model; this makes the problem of confounding by indication less of an issue, although it cannot be ruled out completely. Third, our study has selection bias (prevalence incidence bias) and information bias (follow-up bias).[15] The relatively short period of the occurrence of new risk factors among patients initially having a CHA_2DS_2-VASc score of 0 (male) or 1 (female) could have resulted from an incomplete diagnostic assessment at baseline. Fourth, we were not able to clearly confirm the cause of ischemic stroke, which in some cases could have been due to AF-related

thromboembolism or atherosclerosis and thrombosis of the cerebral artery. Fifth, inaccurate diagnosis of comorbidities can lead to misclassification of CHA_2DS_2-VASc score for intermediate-risk patients with AF. Finally, the OAC group included patients treated with warfarin or non–vitamin K antagonist OACs. The number of non–vitamin K antagonist OAC users was low in this study for the follow-up duration because low-risk patients with AF were included. The non-OAC group would include patients on no antithrombotic therapy or aspirin; the latter is ineffective for stroke prevention in AF and is not safe.[16] In addition, some aspirin use may be "over the counter."

CONCLUSIONS

Low-risk patients with AF should be regularly reassessed to adequately identify patients with incident stroke risk factors that would merit thromboprophylaxis for the prevention of stroke and the composite outcome.

ARTICLE INFORMATION

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Disclosures

None.

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